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Oxidant and Antioxidants During the Transition Period in Dairy Cows

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ABSTRACT

The transition from pregnancy to parturition is associated with metabolic and physiological changes. Oxidative stress is increased in late pregnancy and continue to be higher after parturition, which represent a challenge for the dairy cows to defend the increased free radicals by using the available antioxidants. This review discussed the process of free radical release, the development of oxidative stress and evaluation of the animal health during the transition period and threw the light on different methods used to assess oxidative stress and antioxidants therapy.

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Introduction

The transition period is defined as the transition from pregnancy to parturition and lactation, which extend from the last 3 weeks before to the first 3 weeks after parturition (Bell, 1995). Dairy cattle defense mechanisms are compromised during the transition period due to increased nutrient demands and dysfunction of the immune response (Kehrli *et al.*, 1989; Goff and Horst, 1997) that result in increased the incidence of diseases (Cai *et al.*, 1994; Sordillo *et al.*, 2007) like mastitis, metritis, ketosis and displacements of the abomasum, especially during the first month of lactation (Ingvartsen *et al.*, 2003; LeBlanc *et al.*, 2006).

During the periparturient period, mammary gland prepares for the ensuing lactation and experience extreme shifts in cellular metabolism (Sordillo and Aitken, 2009) that associated with physiological changes that may contribute to altered immune and inflammatory responses including nutritional status and changes in hormone profiles (Sordillo, 2005). The onset of high milk production requires large amounts of molecular oxygen for aerobic metabolism. Therefore, the considerable increase in oxygen requirements during heightened metabolic demands results in increased production of reactive oxygen species (ROS), and associated with the excessive release of free radicals and the progressive development of oxidative stress (Miller *et al.*, 1993; Sordillo, 2005; Sordillo and Aitken, 2009). Indeed, several recent studies showed that production of excess ROS in the peripheral blood can overwhelm certain antioxidant defenses, resulting in increased oxidative stress (Bernabucci *et al.*, 2005; Castillo *et al.*, 2005; Sordillo *et al.*, 2007). Consequently, this review threw the light on the different aspects that related to the involvement of free radicals and oxidative stress in the transition period in dairy cows.

Antioxidants during the transition period

Normally, cells and fluids inside the body contain nutrients and enzymes antioxidants that capable to counteract the free radicals and prevent the development of oxidative stress. Endogenous antioxidants are classified into: Enzyme antioxidants, which include glutathione peroxidase (GSH-Px), catalase and superoxide dismutase (SOD). Vitamin antioxidants, like vitamin E, Beta carotene and vitamin C and ancillary antioxidants, which include glutathione, glutathione reductase and glucose 6-phosphate dehydrogenase (Abd Ellah *et al.*, 2010; Miller *et al.*, 1993).

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At calving, SOD, catalase and GSH-Px enzymes represent the major antioxidant defense components in protecting the cells against increased ROS. Superoxide dismutase catalyzes the dismutation of superoxide radical to hydrogen peroxide, which is further metabolized to water by catalase and GSH-Px enzyme. Several recent studies have shown that the antioxidant capacity in the peripartum period of dairy cows is insufficient to counteract the increase in ROS supply (Bernabucci *et al*., 2005; Castillo *et al*., 2005). Festilă *et al*. (2012) recorded a decrease of mean blood GSH-Px in dairy cows 0–7 days after parturition due to loss of homeostatic control in the postpartum period. On the contorary, some studies reported increase SOD activity on the day of parturition (Bernabucci *et al*., 2005), and after calving (Gaál *et al*., 2006),

There are varieties of sources for nutrient antioxidants, which can be synthesized in the body, derived from the diet or administered parentally. In ruminants, some vitamins as vitamin K can be synthesized by the ruminal and intestinal flora. Also, active form of vitamin D can be synthesized by the effect of the ultraviolet radiation on the skin. In addition, several feedstuffs are also rich in antioxidants, such as vitamin E or precursors of vitamin A (NRC, 2001).

Selenium (Se) is a trace element that is essential for proper intrauterine and postnatal development of calves. Although Se passes both placental and mammary barriers, placental transfer is more effective than the transport of Se into milk (Pavlata *et al*., 2003). The antioxidant GSH-Px protective system depends on the body selenium concentration, which is required for maintenance of biochemical and physiological functions, such as biological antioxidant, immune function, reproduction, and thyroid hormone metabolism (Surai, 2006).
Dietary antioxidants, especially vitamin E and Se, are vital for their ability to contribute to neutralization of ROS, thus hindering the progression toward inflammation. Vitamin E is a potent chain-breaking, lipid-soluble antioxidant (Traber and Stevens, 2011) that interferes with the propagation of free radicals (Traber and Atkinson, 2007), and act by neutralizing free radicals by formation of the prooxidant vitamin E radical, which under normal physiological conditions is regenerated to vitamin E by vitamin C (LeBlanc *et al*., 2004). Vitamin E provides direct protection of membrane lipids, by breaking the self-propagating chain of oxidative damage to the cell membrane. Deficiency of Vitamin E can increase damage to the cells (Sies *et al*., 1992). A decreased plasma level of vitamin E is most commonly encountered in cows at the onset of lactation (Politis, 2012), which may be attributed to decrease hepatic production of different vitamin carrier proteins due to the inflammatory condition of the liver of dairy cows during the transition period (Abd Eldaim *et al*., 2010). These low plasma concentrations of vitamin E through the transition period are also associated with increased incidence of displaced abomasum and fatty liver (Mudron *et al*., 1997).

Effects of oxidative stress on the transition cows

The important physiological and immunological changes that take place as the cow moves through the transition period had been discussed by many authors (Grummer, 1995; Drackley, 1999; Ingvartsen *et al*., 2003; Mulligan and Doherty, 2008). Adaptation of dairy cows during this period is important for guaranteeing efficiency in the dairy industry. failure of the cow to adapt to the increasing demands of the transition period results in metabolic stress. Which is associated with increase fat mobilization (Castillo *et al*., 2006), increase in the production of free radicals that produced in the mitochondria as a normal byproduct of cellular respiration (Halliwell and Gutteridge, 2007), and generation of lipid peroxides and reactive oxygen species (Trevisan *et al*., 2001). Moreover, physiological stresses associated with differentiation of secretory parenchyma are accompanied by a high energy demand and an increased oxygen requirement (Gitto *et al*., 2002). The increased oxygen demand augments the production of oxygen-derived reactants (Halliwell and Gutteridege, 2007).

Dairy cows seemed to have more oxidative stress and low antioxidant defense capacity just before parturition than cows in early lactation, which may contribute to the incidence of many metabolic diseases (Abd Ellah *et al*., 2016), and increases the susceptibility of dairy cows to diseases (Bernabucci *et al*., 2005; Castillo *et al*., 2005, 2006; Sordillo and Aitken, 2009). The increased metabolic demands especially during the peripartal period result in consuming more oxygen through normal cellular respiration in order to provide the energy needed for the onset of lactation. This increase in metabolic activity results in enhanced accumulation of ROS and depletion of important antioxidant defenses around the time of calving (Gitto *et al*., 2002).

Oxidative stress (OS) plays a crucial role in several pathological conditions (Lykkesfeldt and Svendsen, 2007), and usually follow an imbalance between production of reactive oxygen species (ROS) and reduced antioxidant capacity (Valko *et al*., 2007), or when ROS are produced faster than they can be safely counteracted by antioxidant defense (Celi, 2011). Excessive production of free radicals and ROS may lead to damage of biological macromolecules and disrupt normal metabolism and physiology (Trevisan *et al*., 2001), and can induce dysfunction of the immune response (Sordillo, 2013). Furthermore, may contribute to periparturient disorders in dairy cows (Gitto *et al*., 2002), as mastitis, metritis, and retained placenta (Sordillo *et al*., 2007).

Assessment of the oxidative status of dairy cows

Quantification of a separate antioxidant does not provide a good idea on the antioxidant capacity, because the antioxidants act synergically to neutralize the oxidative offence, and the deficiency in one antioxidant does not necessarily indicate that all the antioxidant defense mechanism in impaired. Therefore, several methods have been developed to estimate the total antioxidant capacity. The determination of products of oxidative damage to macromolecules, and antioxidants substances like glutathione and SOD, GSH-Px and catalase are useful markers for evaluating the oxidative stress and antioxidant status. The oxidative destruction of lipids results in lipid peroxidation and releasing malondialdehyde (MDA) as the end product.

Measuring of enzyme and vitamins antioxidants in biological samples is considered one of the popular methods for detection of OS. Antioxidants is the first defense against free radicals, increased antioxidants level reflected increased ROS, and indicate that the body is able to defend against the increased free radicals. Decreased antioxidants levels occurs in cases of diseases associated with destruction of cells or due to overwhelming free radical stress (Abd Ellah, 2010). Detection of oxidative stress could be done also by spectrophotometric measurement of the total antioxidants capacity (TAC), which give an idea about the overall antioxidants levels in the body. This test should be accompanied with measuring MDA level especially in case of decreased TAC.

Malondialdehyde is assayed as a biomarker of OS and it is generated as a consequence of lipid peroxidation. Quantification of MDA in biological fluids in done by using several methodologies, one of them is measuring the thiobarbituric acid reactive substances (TBARS) (Janero, 1990), which are the most commonly used (Bernabucci *et al*., 2002, 2005; Gabai *et al*., 2004; Wullepit *et al*., 2009, 2012; Tanaka *et al*., 2011). TBARS are spectrophotometry method, which is based on the capacity of MDA to react with thiobarbituric acid to produce a red pigment. However, MDA determination has been complained for its low specificity and artefact formation (Celi, 2011), in addition, TBARS are considered inaccurate, as they are not specific for MDA and detect a wide range of lipid peroxidation products (Halliwell and Chirico, 1993). These facts might be behind some of the debated findings of early studies on OS around the time of calving (Castillo *et al*., 2005; Bouwstra *et al*., 2010; Celi, 2011).

Recent studies, reported that detection of oxidative DNA damage in serum (Abd Ellah *et al*., 2014) and in blood lymphocytes (Abd Ellah *et al*., 2016) can be used as a sensitive test to detect OS. The increased oxidative DNA damage indicate that OS affect the DNA and also imply that the body is unable to defend against the increased free radical stress. Both studies were done on cows during the transition period and both of them suggested that the increased oxidative DNA damage was encountered during late prepartum period.

Antioxidant therapy during the transition period

It is necessary to supplement transient dairy cows with vitamins and trace elements, but considering that the requirements for grazing cattle might be lower than their counterparts fed conserved forages. In addition, it is recommended to give an extra supplementation in moments of augmented demands, such as around the time of calving (NRC, 2001).

Supplementing vitamin E in the prepartum period improves the antioxidant capacity, decreases inflammatory production of cytokine, and the incidence of clinical mastitis. In addition, it was reported that vitamin E may improve liver function in transition cows and it is also effective at preventing retained placenta (Bourne *et al*., 2007). Therefore, supplementation of dairy cows with relatively high vitamin E levels is needed to prevent the drop in plasma alpha-tocopherol concentrations around parturition (Spears and Weiss, 2008).

Many authors have also recorded a tendency to transient increase of lipid peroxidation in dairy cows after calving (Mudron and Konvicna 2006; Saleh *et al*., 2007; Sharma *et al*., 2011). This change is typical for this period, and increased intake and higher levels of nutritive antioxidants can efficiently decrease the level of lipid peroxidation (Brzezinska-Slebodzinska *et al*., 1993).

Supplementation of dairy cows with adequate trace mineral and vitamins during the peripartum period is essential to minimize the harmful effects of excessive ROS production (Politis, 2012), improving health status and reducing disease incidence (Bourne *et al*., 2008). It plays an important role in improving the immune responses and in helping the dairy cows to get rid of the stress of early lactation (Spears and Weiss, 2008). Vitamins and certain trace minerals, such as selenium, copper, zinc and manganese have been proven to be effective in counteracting OS and reducing the severity of dairy cattle diseases (Spears and Weiss, 2008; Bouwstra *et al*., 2009; Sordillo and Aitken, 2009). Castillo *et al*. (2013) suggested that supplementation of minerals and vitamins above the reported requirements can improve animal health and performance. However, Bouwstra *et al*. (2010) reported that when supplementation of nutrients exceeds certain level, it can cause harmful effects.

The most commonly used method for antioxidant supplementation in commercial dairy farms is the addition of vitamins and minerals to the diet of the animals, especially in the form of premixes added to the mixed ration. Another method is done by injection of vitamins and trace minerals especially to animals during the transition period and in farms with a number of animals not large enough to implement practically a specific diet for close-up dry cows.

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